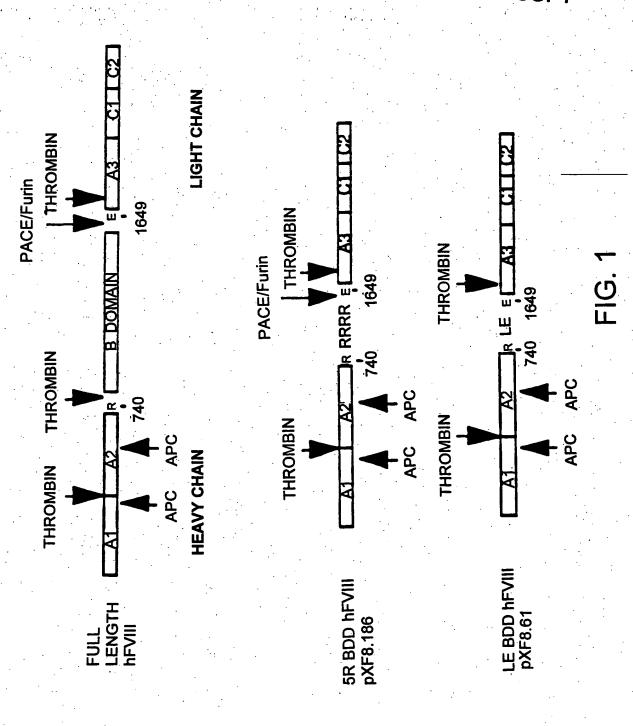


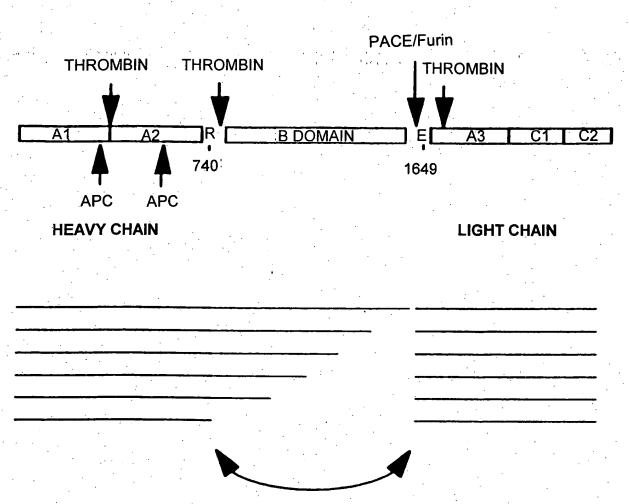
Page 1 of 33 OPTIMIZED MESSENGER RNA 09/407,605 10278-009001 REPLACEMENT SHEET

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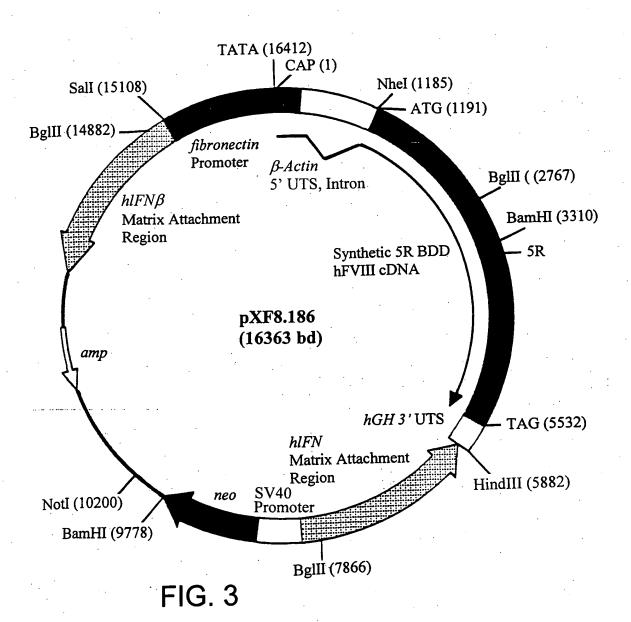
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REPLACEMENT SHEET

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HETEROGENEITY OF hFVIII IS DUE TO PROTEOLYSIS WITHIN THE B-DOMAIN

FIG. 2



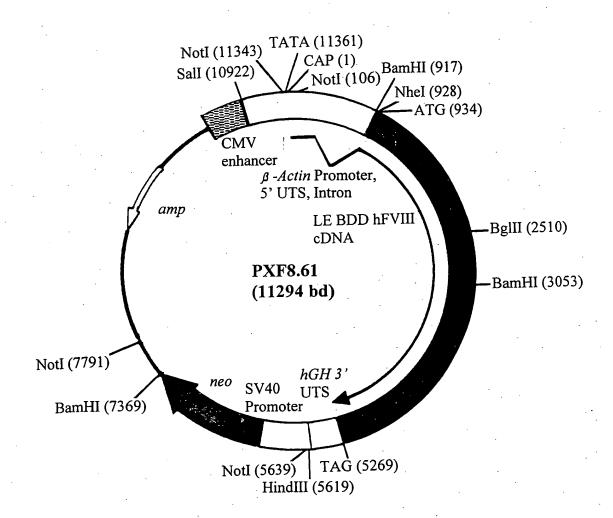


FIG. 4

Fragment A

E8A

Nhel

AM1 Af1

CATCTTAAGCATCCGATCGTACGTCTAGCTCGACTCGTGGACGAAGAAGAAGACGCGACGACGCGAAGAAGACG GTAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGCGCTTCTTGC

AM1 Ar3

3, OH 5, P

3, OH

AM1 Af2

AM1 Ar2

CCCGCTCGACGGGCACCTGCGGGGGGGGGGGGGCGCACGGGTTCTCGAAGG GGAAGTTGTGGTCGCA GGGCGAGCTGCCCGTGGACGCCCGCTTCCCCCCCCCGCGTGCCCAAGAGCTTCCTCCTTCAACACCAGCGT

3. OH 5' P

AM1 Af3

GGTGTACAAGAAGAC CCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCCGCCCCCC

AM1Ar1

FIG. 5A

CTGGATGGGCCTGCTGGGCCCC TACAAGCTTTAC GACCTACCCGGACGACCCGGGG: ATCTTCGAAATG Hud Apal

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Fragment B

GTAGAATTCGTAGGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAG CATCTTAAGCATCCCCGGGGTGGTAGGTCCGGCTCCACATGCTGTGGCACCACTAGTGGGACTTCTTGTACCGGTC

AM1Bf1

AM1.Br3

3. OH 5' P

Geregegeactice eacerecegeaccegeactegareac_circegicectecegegegereargeregeter CCACCCCGTGAGC TTGCACGCCGTGGCCGTGAGCTACTG GAAGGCCAGCGAGGCCGCCGAGTACGACGACAGA

5. P 3. OH

AM1Br2

3. OH 5. P

ccagccagcgagaaggacgacaaggtgttccccgg~cggcaccaccacctacgtgtggcaggtg ctgaag GGTCGGTCGCTCTTCCTCTGCTGTTCCACAAGGGGCC GCCGTCGGTGTGGATGCACACCGTCCAC_GACTTC

5. P 3. OH AM1Bf2

AM1Bf3

Pm

CTCTTGCCGGGGTACCGGTCGCTGGGGGACACGGACTGGATGTCGATGGACTCGGTGCACGATGTTCGAAATG GAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTACAGCTACCTGAGCCTGAGCCTACAAGCTTTAC

AM1 Br1

FIG. 5B

GTAGAATTCGTAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGCCCTGCTGGTGTGCCGCGAGGGCAGCCTG CATCTTAAGCATCGGTGCACCTGGACCACTTCCTGGACTTGTCGCCGGACTAGCCGCGGGACGACCACACGGCGCTCCCGTCGGAC PmI EcoRi

AM1C1

AM1 Cr3

cggttcctcttctq getctggacgtgttcaagtag_gacgacaagcggcacaagctgctcccgttctcgaccgtgtcgttctgg GCCAAGGAGAAGAC CCAGACCCTGCACAAGTTCATC CTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACC AM1 Cf2 3. OH 5. P

3. OH 5. P

AAGAACAGCCTGATGCAGGACCGCGACGCCCAGCGCCCTGGCCCTAGGATGCACAC CGTGAACGGCTACGTGAACCGC TICTIGICGACTACGICCTGCGCGCGGCGGTCGCGGG CGCGGACCGGGTICTACGIGIGGCACTIGCCGAIGCACTITGGCG

TCGGACGGCCGGACTAGCCGACGGTGCGTTCTCGCACATGACCGTGCACGATGTTCGAAATG AGCCTGCCCGGCCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGCTACAAGCTTTAC AM1Cf3

AM1C1

FIG. 5C

Hudill

Pml

PHI **尼8**四

GTAGAATTCGTAGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCACAGCATCTTCCTGGAGGGCCACACTCTTCCTGGTGCGCAACCACCG CATCTTAAGCATCGTGCACTAGCCGTACCCGTGGTGGGGGCTCCACGTGTCGTAGAAGGACCTCCCGGTGTG GAAGGACCACGCGTTGGTGGC 3, OH AM1Dr4

AM1Df1

AM1Df2 3, OH 5, P

GGTCCG_GTCGGACCTCTAGTCGGGGTAGTGGAAGGACTGGGGACGACTACCTGGACCGGTCAAGGACGACAA GACGGTGTAGT
AM1Dr3
5' P 3' OH GCAGCCACCAGCAC GACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCCCAGCTGCGCATGAAGAACAACGAGGAGGTCC AM1Df3 3. OH 5' P

CGTCGGTGGTCGTG_CTGCCGTACCTCCGGATGCACTTCCACCTGTCGACGGGGCTCGTCGGGGTCGACGCGTACTTCTTGTTGCTCCTCC qG 5. P 3. OH BamH GAGGACTACGACGACGACCTGAC CGACAGCGAGATGGACGTGGTGCGTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCTCTACGGAT CTCCTGATGCTGCTGCTGGACTG_GCTGTCGCTCTACCTGCACCACGCGAAGCTGCTGTTGTCGGGGTCGAAGTAGGTCTAGAGATGCCTA AM1Df4 AM1Dr2 3. OH 5' P

AM1Dr1

CCTACAAGCTTTAC GGATGTTCGAAATG Hudil

BamHI <u>E89</u>

CATCTTAAGCATCCCTAGGCGTCGCACCGGTTCTTCGTGGGGTTCTGGACCCACGTGATGTAGCGGCGGCTCCTCCTCCTGACCCTGATGCG GTAGAATTCGTAGGGATCCGCAGCGTGGCCAAGAAGCACCCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGC

AM1Ef1

AM1Er4

3, OH 5' P

cccctg Grectgecccccgacgacgccda cracaagaccagraccrgaacaacgcccccagcgcarcgccaagcgaagracaaga GGGGGAÇ ÇACGACCGGGGGCTGCTGGCGTC_GATGTTCTCGGTCATGGACTTGTTGCCGGGGGTCGCGTAGCCGGCGTTCATGTTCTTCCA AM1Er3

3. OH 5' P

Apal

GCGCTTCATGGCCTACACCGACGAGACCTTCAAGACCC GCGAGGCCATCCAGCACGAGAG CGGCATCCTGGGCCCCCTGCTGTACGGCGA CGCGAAGTACCGGATGTGGCTGCTCTGGAAGTTCTGGG ÇGCTCCGGTAGGTCGTGCTCTC_GCCGTAGGACCCGGGGGACGACATGCCGCT AM1Ef2

AM1Ef3 5. P 3. OH

3, OH 5, P

ggigggcgacacccigcigaicaicticaagaaccaggccagccgccctacaacaiciacciccacggcaicaccaacgacgigci CCACCCGCTGTGGGACGACTAGTAGAAGTTCTTGGTCCGGTCGGGGGATGTTGTAGATGG GGGTGCCGTAGTGGCTGCTGCACGCG_GGGGA

AM1 E2

BgIII

Hudil

CATGTCGGCGGCGGACGGGTTCCCGCACTTCGTGGACTTCCTGAAGGGGTAGGACGGGCCGCTCTAGAGATGTTCGAAATG GTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTCTACAAGCTTTAAC

AM1Ef4

AM1E1

FIG. 5E

Fragment F

GTAAAGCTTGTAGGGTACCAGCTGCGGTTCTCGTCGAACACGCTGAACAGGATCACGTTGC TGCTTGTCGCTCATGATCTGGTTGCC AM1F11 Kpnl Hindill

3'OH 5'P AM1 Ff2 decreerce control of contro c_gegaccaggregagagaacategtetagtegeeceggetagtecggegaccggtecagegaggtacaaggtacaagte cttegae

CTGTAGTAGCGGGTCAG GCAGCGGGGTCGCTCTTGGTGGGGCCGTCCTCCACGGTCACGGTCCACTTGTACTTGAAGATCTCTAC GACATCATCGCCCAGTC_CGTCGCCCCCAGCGAGAACCACCCCGGCAGGAGGTGCCAGTGCCAGGTGAACATGAACTTCTAGAGATG BgIII AM1Ff3 **AM1 Fr2** 3. OH 5' P

AM1 Fr1

FIG. 5F

EcoRi

GAATTCTAC CTTAAGATG

Fragment G

Kpnl

E S S S

AM1Gf1

GTAGAATTCGTAGGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGGCGTGCAGCTGGAGGACCCCCGAGTTCCAGGCCAG CATCTTAAGCATCCCATGGACTGGCTCTTGTAGGTCGCGAAGGACGGGTTGGGGCGGCCGCACGTCGACCTCCTGGGGCTCAAGGTCCGGTC

AM1Gr3

3'OH 5'P

CAACAT CATGCACAGCATCAACGGCTAC GTGTTCGACAGCCTGCAGGTGACGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAG GTTGTA GTACGTGTCGTAGTTGCCGATG_CACAAGCTGTCGACGTCGACTCGCACACGGACGTGCTCCACCGGATGACCATGTAGGACTC AM1Gf2 **AM1Gr2** 5, P 3, OH

3. OH 5. P

GTAGCCGCGCGCTCTGGCTCAAAGGACTCGCACAAGAAGTCG CCGATGTGGAAGTTCGTGTTCTAC_CACATGCTCCTGTGGGACTGGGACAA CATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCTGGCTACACCTTCAAGCACAAGATG GTGTACGAGGACACCCTGACCTGTT 5. P. 3. OH

FIG. 5G

GGGGAAGTCGCCCCTCTGGCACAAGTACTCGTACCTCTTGGGGCCGGACACCTAGGGATGTTCGAAATG CCCCTTCAGCGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCCTACAAGCTTTAC BamHI AM1Gf3 AM1Gr1

Fragment H

CATCTTAAGCATCCCTAGGACCCGACGGTGTTGTCGCTGAAGGCGTTTGGCGCCGTACTGGCGGGACGACTTCCACTCGTCGAÇ GCTGTTCTTGTGGCCGCTG GTAGAATTCGTAGGGATCCTGGGCTGCCACAACAGCGACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGTCGACAAGAACACCGGCGAC **AM1Hf1** BamHI

TACTACGAG GACAGCTACGAGGACATCAGCGCCTACCTGCTGAGCAAGAACAACGCCCATCGAGCCCCGGCCTGGAGGAGATCACCCGGCAC CACCCTGCAGAG **AM1Hf2** AM1Hr4 3. OH 5' P

ATGATGCTC_CTGTCGATGCTCCTGTAGTCGCGGATGGACGACTCGTTCTTGTTGCGGTAGCTCGGGGCGGACCTCCTCTAGTGGGCGTG GTGGGACGTCTC CGACCAGGAG GAGATCGACTACGACGACACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCC^CCGCAGCT GCTGGTCCTC_CTCTAGCTGATGCTGTGGTAGTCGCACCTCTACTTCTTCCTCTGAAGCTGTAGATGCTGCTCCTGCTCTTGGTCTTCGGG_GGCGTCGA AM1Hf3 AM1Hr3 3. OH 5. P

3' OH 5' P Hindill Hindill TCCAGAAGAAGACC CGCAGTGGAGCGCCTGTGGGACTACGGCATGAGCAGCCCCCACGTGCTACAAGATTAC **AGGTCTTCTTCTGG_GCGGTGATGAAGTAGCGGCGCGCACCTCGCGGACACCCCTGATGCCGTACTCGTCGGGGGTGCACGATGTTCGAAATG** AM1Hr1

AM1Hr2

FIG. 5H

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Fragment |

5 P 3 OH	BstEll	ccctgtaccg' decgagetgaacgageacctggeectgetgggeecetacatecgeecgaggaggaggagaacateatggtgaecgtgeaggagttegTe	36GGACATGGCG_CCGCTCGACTTGCTCGTGGACCCGGACGACCGGGGATGTAGGCGCGCTCCACCTCCTGTTGTAGTACCACTGGCACGTCCTCAAGC	5, P 3, OH
	AM1 If 2	CATCCGCGCCGAGGTGGAGGACAACA	STAGGCGCGCTCCACCTCCTGTTGT.	
AM1 Ir4	Apal	BAGCACCTGGCCTGCTGGCCCCTAC	CTCGTGGACCCGGACGACCCGGGGATC	AM1 lr3
	3. OH 5. P	cccrgracce deceasersaace	GGGGACATGGCG_CCGCTCGACTTGC	ı

3'OH 5'P AM1 If 3	CTGTTCTTCACCATCTTCGAC GAGACCAAGAGCTGGTACTTCACCGAGAACATGGAGCGCAACTGCCGCGCCCCCTGCAACATCCAGATGGAGGACC TCCACC	GACAAGAAGTGGTAGAAGCTG_CTCTGGTTCTCGACCATGAAGTGGCTCTTGTACCTCGCGTTGACGGCGCGGGGGACGTTGTAGGTCTACCTCCTGG GGTGG	AM1 Ir 2 5. P 3. OH
3,0	CTGTTCTTCACCATCTTCG	GACAAGAAGTGGTAGAAGC	

Kpul Hlag	GGTACCCTACAA	CCATGGGATGTT	
	TICAAGGAGAACTACCGCTICCACG CCATCAACGGCTACATGGACACCCTGCCCGGCCTGGTGATGGCCCAGGACCAGCGCATCCGCTGGTACCTACAA	AAGTICCICITGAIGGCGAAGGIGC GGIAGIIGCCGAIGIAGIACIGIGGACGGGCCGGACCACIACCGGGICCIGGICGCGIAGGCGACCAIGGAIGII	DM1171
	TTCAAGGAGAACTACCGCTTCCACG CCATCAACGGCTACAT	AAGTTCCTCTTGATGGCGAAGGTGC_GGTAGTTGCCGATGTA	

CTTTAC

F (C)

Bst Ell ExoRi

GTAGAATTCGTAGGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGCGCC CATCTTAAGCATCCCACTGGAAGGCGTTGGTCCGGTCGGCGGGGATGTCGAAGATGTCGTCGGACTAGTCGATGCTCCTCCTCGTCGCGG

AM1 Jr3

3. OH 5. P

AM1 Jf2

AGG TCCCCCAAGCCCCCCCAAGAACTTC GTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCACCACATGGCCCCCACAA TCC CGCGGCTCGGGGCGTTCTTGAAG_CACTTCGGGTTGCTCTGGATGAAGACCTTCCACGTCGTGGTGTACCGGGGGGTGTT a, OH

AM1 Jr2

3'OH 5'P GGACGAGITCGACTGCAAGGCCTGGGCCTACTTCAG CGACGTGGACCTGGAGAAGGAC dTGCACAGGGGCCTGATCGGCCCCCTGCTG CCTGCTCAAGCTGACGTTCCGGACCCGGATGAAGTÇ GCTGCACCTGGACTTCCTG_CACGTGTCGCCGGACTAGCCGGGGGACGAC

Eagl AM1Jf3

Hind **Bst Ell**

GTGTGCCACACCAACACCCTGAACCCCGCCCACGGCCGCCAGGTGACCCTACAAGCTTTAC CACACGGTGTGGTTGTGGGACTTGGGGCGGGTGCCGGCGGTCCACTGGGATGTTCGAAATG

Fragment K

Kpnl Ecol

Pm **AM1Kf1**

CATCTTAAGCATCCCATGGACGACTCGTACCCGTCGTTGCTCTTGTAGGTGTGGTGAAGTCGCCGGTGCACAAGTGGCACGCGTTCTT GTAGAATTCGTAGGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGCGCAAGAA

AM1Kr3

3. OH 5' P

GGAG GAGTACAAGATGGCCCTGTACAAC CTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGT CCTÇ ÇTCATGTTCTACCGGGACATGTTG_GACATGGGGCCGCACAAGCTCTGGCACCTCTACGACGGGTCGTTCCGGCCGTAGACCGCGCA **AM1Kf2 AM1Kr2** œ, Θ, ы 2

3'OH 5'P GGAGTGCCTGATCGCGAGCACCTGCCGGCATGAGTCACCCTGTTCCTGGTGTACAG CAACAAGTGCCAGACCCCCTGGGCATGGC 5. P 3. OH

AM1Kf3

Hudiii Apal

CAGCGGCCACATCCGCGACTTCCAGATCACCGCCAGCGGCCAGTACGGCCCAGTGGGCCCTACAAGCTTTAC GTCGCCGGTGTAGGCGCTGAAGGTCTAGTGGCGGTCGCCGGTCATGCCGGTCACCCGGGGATGTTCGAAATG

FIG. 5X

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Fragment

Apai

尼8 图

GTAGAATTCGTAGGGCCCCCCAAGCTGGCCCGCCTGCACTACAGCGCCAGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAG CATCTTAAGCATCCCCGGGGGTTCGACCGGGCGGACGTGATGTCGCCGTCGTAGTTGCGGACCTCGTGGTTCCTCGGGAAGTCGACCTAGTTC

AM1Lr3

GTGGAC CTGCTGGCCCCCATGATCATC CACGGCATCAAGACCCAGGGCGCCCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCA CACCTG GACGACCGGGGGTACTAGTAG_GTGCCGTAGTTCTGGGTCCCGCGGCGGTCTTCAAGTCGTCGGACATGTAGTCGGTCAAGTAGT 3, OH

AM1Lr2

3. OH 5. P

TCATGTACAGCCTGGACGGCAAGAAGTG GCAGACCTACCGCGGCAACAGCAC CGGCACCCTGATGGTGTTCTTCGGCAACGTGGACAGCAG AGTACATGTCGGACCTGCCGTTCTTCAÇ CGTCTGGATGGCGCCGTTGTCGTG_GCCGTGGGGACTACCACAAGAAGCCGTTGCACCTGTCGTC 5, P 3, OH

CGGCATCAAGCACAACATCTTCAACCCCCCCGGGCTACAAGCTTTAC GCCGTAGTTCGTGTTGTAGAAGTTGGGGGGGCCCCGATGTTCGAAATG Smal AM1Lf3

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Fragment M

EcoRI EcoRV

AM1Mf1

GTAGAATTCGTAGGATATCATCGCCCGCTACATCCGCCTGCACCCCACCACTACAGCATCCGCAGCACCCTGCGCATGGAGCTGATGGG

AM1Mr3

3. OH 5. P

AM1Mf2

CTGCGAC TTGAACAGCTGCAGCATGCCCCTGG GCATGGAGAGCAAGGCCATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACC GACGCTG GACTTGTCGACGTCGTACGGGGACC_CGTACCTCTCGTTCCGGTAGTCGCTGCGGGTCTAGTGGCGGTCGTCGATGAAGTGG

5, P 3, OH

3. OH 5. P

AACATGTTCGCCACCTGGAGCCCCAGCAAGGCCTCGCCTGCAGGGCCGCAG CAACGCCTGGCGCCCCCAGGTGAACAACCCCA TTGTACAAGCGGTGGACCTCGGGGTCGTTCCGG GCGGACGTGGACGTCCCGGCGTC_GTTGCGGACCGCGGGGGTCCACTTGTTGGGGGT

5, b 3, OH

AM1Mf3

Bst Ell Hindill

AGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCCTACAAGCTTTAC TCCTCACCGACGTCCACCTGAAGGTCTTCTGGTACTTCCACTGGGATGTTCGAAATG

MIMI

FIG. 5M

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Fragment N

Bst Ell

E8B

CATCTTAAGCATCCCACTGGCCGCACTGGGTCCCGCACTTCTCGGACGACGACGTCGTACATGCACTTCCTCAAGGACTAGTCGTCGTCGGTCCTGCC GGT 5. P 3. OH GTAGAATTCGTAGGGTGACCGGCGTGACCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCAGCCAGGACGG TCCA

AM1Nf1

AM1Nf2

3. OH 5. P

GGCGATGGACGCGTAGGTGGG_GGTCTCGACCACGTGGTCTAGCGGGACGCGTACCTCCACGACCCGACGCTCCGGGTCCTGGACATGATCGACGGGCCCGAT Smal AM1Nf3 **AM1Nr1** 3. OH 5' P

Hindill

CAAGCTTTAC GTTCGAAATG

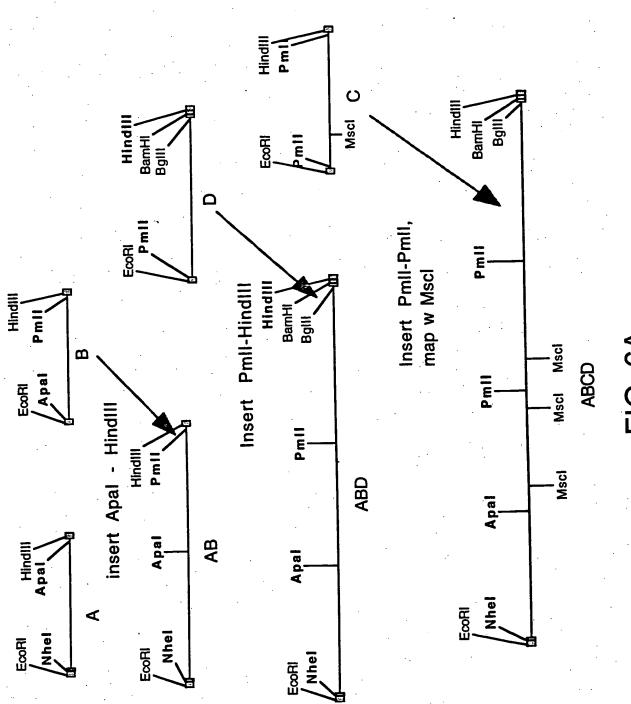
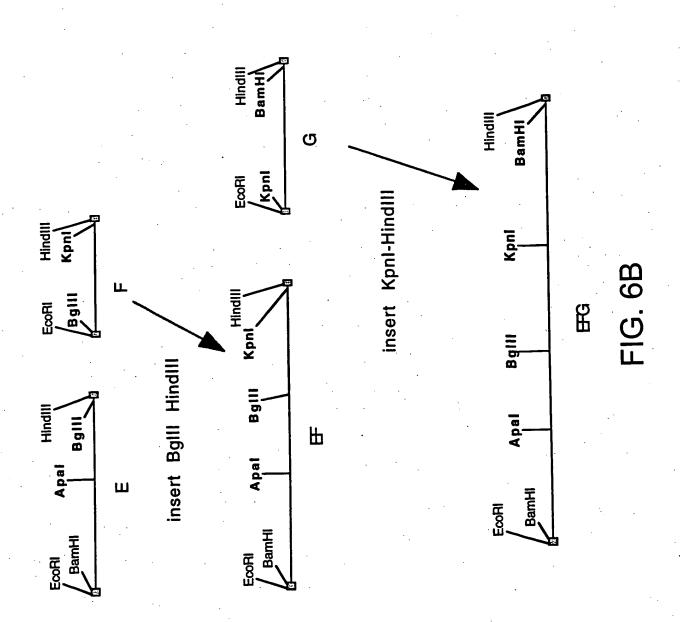
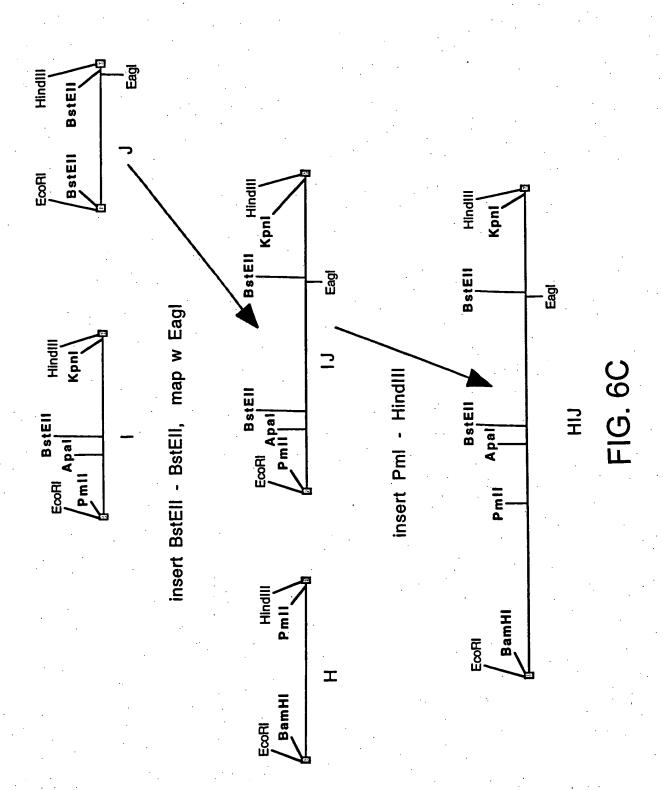
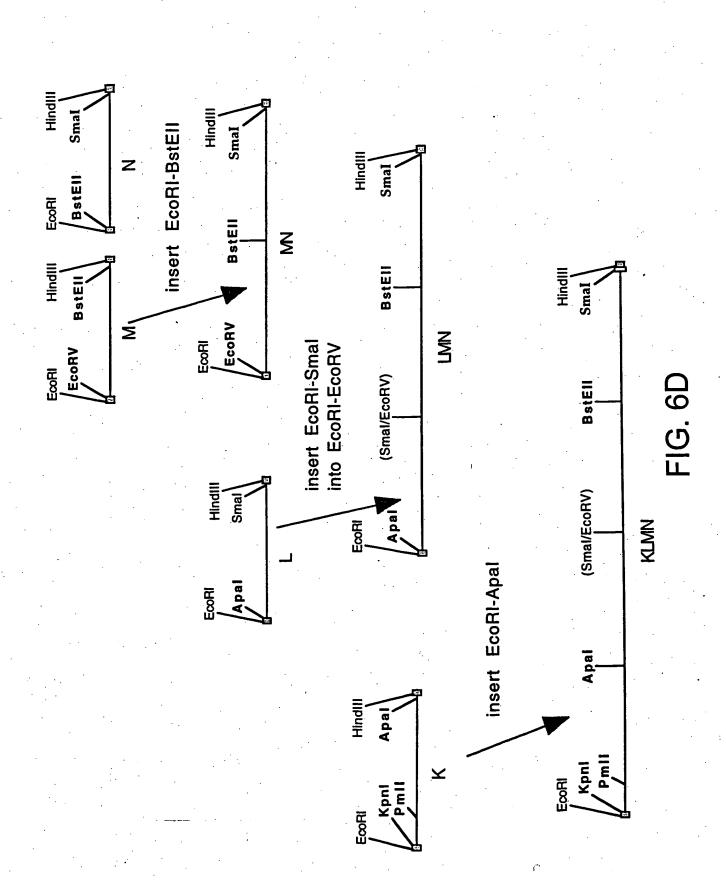
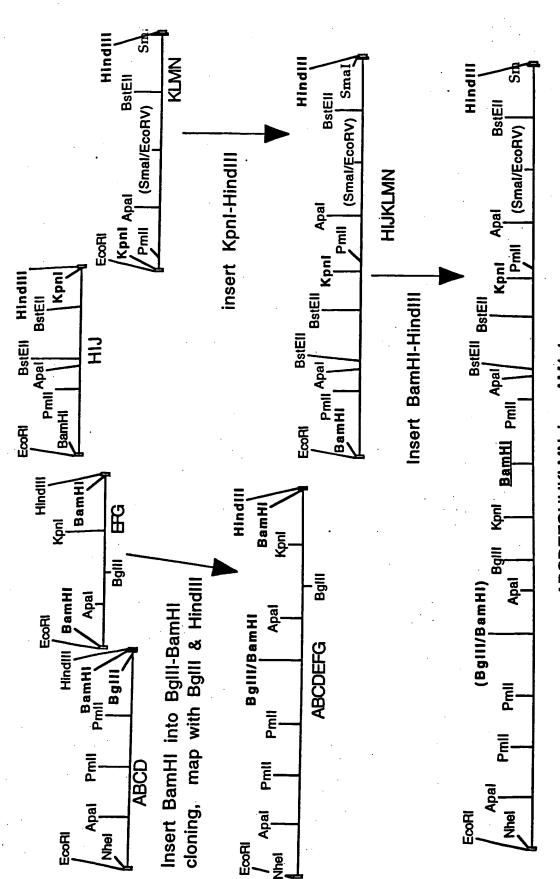


FIG. 6A









ABCDEFGHIJKLMN, i.e. pAM1-1

FIG. 6E

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	The Nicol
_	ECORI Nhei
1	TAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGCGCTTCTGCTTC
_	1 MetGlnIleGluLeuSerThrCysPhePheLeuCysLeuLeuArgPheCysPhe
	AGCGCCACCCGCCGCTACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGAGCGACCTGGGCGAG
	SerAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSerTrpAspTyrMetGlnSerAspLeuGlyGlu
	CTGCCCGTGGACGCCCGCTTCCCCCCCCGCGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAG
	LeuProValAspAlaArgPheProProArgValProLysSerPheProPheAsnThrSerValValTyrLys
	AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCCGCCCCCCTGGATGGGCCTG
6.7₽	LysThrLeuPheValGluPheThrAspHisLeuPheAsnIleAlaLysProArgProProTrpMetGlyLeu
	Apal Mscl
	$\tt CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCA$
-	GTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACCAGACCAGC
	ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSerGluGlyAlaGluTyrAspAspGlnThrSer
	ValserLeunisatavaldiyvalsetiyttiphysatasetdiudiyatadiutytaspaspdiitiitset CAGCGCGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAGGAG
	CAGCGCGAGAAGGACGACGACGAGGGGTTTCCCCGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAGGAGGTGAAGGAGGTGAAGGAGGAGGTGAAGGAGGA
139	Msci PmII
EOE	AACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGAC
	AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSerTyrLeuSerHisValAspLeuValLysAsp
103,	Mscl
577	CTGAACAGCGGCCTGATCGGCGCCCTGCTGGTGTGCCGCGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACC
•	LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGluGlySerLeuAlaLysGluLysThrGlnThr
	CTGCACAAGTTCATCCTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGC
	LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGlyLysSerTrpHisSerGluThrLysAsnSer
721	CTGATGCAGGACCGCGACGCCCAGCGCCCGCGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAAC
235▶	${\tt LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpProLysMetHisThrValAsnGlyTyrValAsnG$
	PmII
	$\tt CGCAGCCTGCCCGGCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACCACCGCAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACCACCACCACCACCACCACCACCACCACCACC$
	${\tt ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerValTyrTrpHisValIleGlyMetGlyThrThrough SerValTyrTrpHisValIleGlyMetGlyThrThrough SerValIleGlyMetGlyThrThrough SerValIleGlyMetGlyThrThrough SerValIleGlyMetGlyThrThrough SerValIleGlyMetGlyThrThrough SerValIleGlyMetGlyThrThrough SerValIleGlyMetGlyMetGlyThrThrough SerValIleGlyMetGl$
•	$\tt CCCGAGGTGCACAGCATCTTCCTGGAGGGCCACACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGAGGCCAGCCTGGAGGCCAGCCA$
	${\tt ProGluValHisSerIlePheLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisA$
	${\tt ATCAGCCCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCACCACCACCACCACCACCACCACCACCACCACCA$
307▶	IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMetAspLeuGlyGlnPheLeuLeuPheCysHis
1009	ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCCCAGCTG
	IleSerSerHisGlnHisAspGlyMetGluAlaTyrValLysValAspSerCysProGluGluProGlnLeu
	CGCATGAAGAACAACGAGGAGGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGC
355	ArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspLeuThrAspSerGluMetAspValValArg
-	(BgIII/BamHI)
	TTCGACGACGACACAGCCCCAGCTTCATCCAGATCCGCAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTC
-	PheAspAspAspAsnSerProSerPheIleGlnIleArgSerValAlaLysLysHisProLysThrTrpVal
	CACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACCGCAGCTAC
403	HisTyrIleAlaAlaGluGluAspTrpAspTyrAlaProLeuValLeuAlaProAspAspArgSerTy
4007	Eagl
	AAGAGCCAGTACCTGAACAACGGCCCCCAGCGCATCGGCCGCAAGTACAAGAAGGTGCGCTTCATGGCCTACLysSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyArgLysTyrLysLysValArgPheMetAlaTyr
421	LysserGinTyrLeuAshAshGiyProGinArgileGiyArgLysTyrLysLysVaiArgFnemeCA1ary
	AUGI

1369 ACCGACGAGACCTTCAAGACCCGCGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGC 451 ThraspGluThrPheLysThrargGluAlaIleGlnHisGluSerGlyIleLeuGlyProLeuLeuTyrGly

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- 1441 GAGGTGGGCGACACCCTGCTGATCATCTTCAAGAACCAGGCCAGCCGCCCCTACAACATCTACCCCCACGC
 475 GluValGlyAspThrLeuLeuIleIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly
 1513 ATCACCGACGTGCGCCCCCTGTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATC
 499 IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle
 BgIII
- 1585 CTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGCCCCACCAAGAGCGACCCCCGC
 523 LeuProGlyGluIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg
 1657 TGCCTGACCCGCTACTACAGCAGCTTCGTGAACATGGAGCGCGACCTGGCCAGCGGCCTGATCGGCCCCCTG
 547 CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu
 1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCGGCAACCAGATCATGAGCGACAAGCGCAACGTGATCCTG
 571 LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu
- Kpnl

 1801 TTCAGCGTGTTCGACGAGAACCGCAGCTGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGCC
 595 PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla

 1873 GGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTCGAC
 619 GlyValGlnLeuGluAspProGluPheGlnAlaSerAsnIleMetHisSerIleAsnGlyTyrValPheAsp

 1945 AGCCTGCAGCTGAGCGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGAC
 643 SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTrpTyrIleLeuSerIleGlyAlaGlnThrAsp

 2017 TTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTC
 667 PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe
- 2089 CCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCTGGGCTGCCACAACAGC
 691 PropheserGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer
 2161 GACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGCGACAAGAACACCGGCGACTACTAC
 715 AspPheArgAsnArgGlyMetThrAlaLeuLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr
 2233 GAGGACAGCTACGAGGACATCAGCGCCTACCTGCTGAGCAAGAACAACGCCATCGAGCCCCCGCCTGGAGGAG
 739 GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAsnAlaIleGluProArgLeuGluGlu
 BstXI
- 2305 ATCACCCGCACCACCCTGCAGAGCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAGATGAAG
 763 IlethrargthrthrLeuGlnSerAspGlnGluGluIleAspTyrAspAspThrIleSerValGluMetLys
 2377 AAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCCGCAGCTTCCAGAAGAAGACCCGCCAC
 787 LysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysLysThrArgHis
- 2449 TACTTCATCGCCGCCGTGGAGCGCCTGTGGGACTACGGCATGAGCAGCAGCCCCCACGTGCTGCGCAACCGC 811 TyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerSerProHisValLeuArgAsnArg 2521 GCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAG 835 AlaGlnSerGlySerValProGlnPheLysLysValValPheGlnGluPheThrAspGlySerPheThrGln
- 2593 CCCCTGTACCGCGGCGAGCTGAACGAGCACCTGGGCCTGCTGGGCCCTACATCCGCGCCGAGGTGGAGGAC 859 ProLeuTyrArgGlyGluLeuAsnGluHisLeuGlyLeuLeuGlyProTyrIleArgAlaGluValGluAsp BstEII
- 2665 AACATCATGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAG
 883 AsnileMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSerTyrGlu
 2737 GAGGACCAGCGCCAGGGCGCCGAGCCCCGCAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGG
 907 GluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyrPheTrp
 2809 AAGGTGCAGCACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTG
 931 LysValGlnHisHisMetAlaProThrLysAspGluPheAspCysLysAlaTrpAlaTyrPheSerAspVal

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2881 GACCTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCCAACACCCTGAACCCC 955 AspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeuAsnPro **BstEll** 2953 GCCCACGGCCGCCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAGAGCTGG 979 AlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLysSerTrp 3025 TACTTCACCGAGAACATGGAGCGCAACTGCCGCGCCCCCTGCAACATCCAGATGGAGGACCCCACCTTCAAG $1003 \blacktriangleright \texttt{TyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThrPheLysAsnIleGlnMetGluAspProThrPheLysAsnIleGlnM$ 3097 GAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGCCTGGTGATGGCCCAGGAC 1027 GluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAlaGlnAsp Pmli 3169 CAGCGCATCCGCTGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCAC 1051 GlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSerGlyHis 3241 GTGTTCACCGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTCGAGACC 1075 ValPheThrValArgLysLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPheGluThr 3313 GTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGC 1099 ValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHisAlaGly 3385 ATGAGCACCCTGTTCCTGGTGTACAGCAACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCCGC 1123 MetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHisIleArg Apai 3457 GACTTCCAGATCACCGCCAGCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCCGCCTGCACTACAGCGGC 1147 AspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyrSerGly 3529 AGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATC 1171 SerileAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMetIleIle 3601 CACGGCATCAAGACCCAGGGCGCCCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTAC 1195 hisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIleMetTyr 3673 AGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAAC 1219 SerLeuAspGlyLysLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePheGlyAsn (Smal/EcoRV) 3745 GTGGACAGCAGCGGCATCAAGCACATCTTCAACCCCCCCATCATCGCCCGCTACATCCGCCTGCACCCC 1243 ValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeuHisPro 3817 ACCCACTACAGCATCCGCAGCACCCTGCGCATGGAGCTGATGGGCTGCGACCTGAACAGCTGCAGCATGCCC 1267 ThrHisTyrSerIleArgSerThrLeuArgMetGluLeuMetGlyCysAspLeuAsnSerCysSerMetPro 3889 CTGGGCATGGAGAGCCAACGCCATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACCAACATGTTCGCC 1291 LeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMetPheAla 3961 ACCTGGAGCCCCAGCAAGGCCCGCCTGCACCTGCAGGGCCGCAGCAACGCCTGGCGCCCCCAGGTGAACAAC 1315 ThrtrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnValAsnAsn 4033 CCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAG 1339 ProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGlyValLys 4105 AGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTG 1363 SerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerSerGlnAspGlyHisGlnTrpThrLeu 4177 TTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTG 1387 PhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsnSerLeu 4249 GACCCCCCCTGCTGACCCGCTACCTGCGCATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGCGCATG 1411 AspProProLeuLeuThrArgTyrLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeuArgMet SmaI.

4321 GAGGTGCTGGGCTGCGAGGCCCAGGACCTGTACTAGCTGCCCGGGCTACAAGCTTT

1435 GluValLeuGlyCysGluAlaGlnAspLeuTyr • • •

FIG. 7C

HindIII

BamHI E88

CATCTTAAGCCTAGGACCCGACGGTGTTGTCGCTGAAGGCGTTGGCGCCGTACTGGCGGGACGACTTCCACTCGTCGACGCTGTTCTTGTGGCCGCTGATGATG

AM8R4

AM8FR2

3. OH 5' P

3. OH 5. P

CGCTGGTCCTCCTCTAGCTGATGCTGCTGTGGTAGTCGCACCTTCGAAATG GCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAAGCTTTAC Hindill **Bst XI** AM8F4

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	EcoRI Nhei	
1	TAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGCGCTTCTGCTTC	
	1 MetGlnIleGluLeuSerThrCysPhePheLeuCysLeuLeuArgPheCysPhe	
73	AGCGCCACCCGCCGCTACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGAGCGACCTGGGCGAG	
19	SerAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSerTrpAspTyrMetGlnSerAspLeuGlyGlu	
145	CTGCCCGTGGACGCCCGCTTCCCCCCCCGCGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAG	
	LeuProValAspAlaArgPheProProArgValProLysSerPheProPheAsnThrSerValValTyrLys	
217	AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCCGCCCCCCTGGATGGGCCTG	
	LysThrLeuPheValGluPheThrAspHisLeuPheAsnIleAlaLysProArgProProTrpMetGlyLeu	
•	Apal Mscl	
289	CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCA	
	LeuGlyProThrIleGlnAlaGluValTyrAspThrValValIleThrLeuLysAsnMetAlaSerHisPro	
	GTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACCAGACCAGC	
	ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSerGluGlyAlaGluTyrAspAspGlnThrSer	
	CAGCGCGAGAAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAGGAG	
	GlnArgGluLysGluAspAspLysValPheProGlyGlySerHisThrTyrValTrpGlnValLeuLysGlu	
100	Msci	
505	AACGGCCCCATGGCCAGCGACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGAC	
	AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSerTyrLeuSerHisValAspLeuValLysAsp	
	Mscl	
577	CTGAACAGCGGCCTGATCGGCGCCCTGCTGGTGTGCCGCGAGGGCCAGCCTGGCCAAGGAGAAGACCCAGACC	
187▶	LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGluGlySerLeuAlaLysGluLysThrGlnThr	
649	CTGCACAAGTTCATCCTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGC	:
	LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGlyLysSerTrpHisSerGluThrLysAsnSer	
721	CTGATGCAGGACCGCGACGCCCAGCGCCCGCGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAAC	;
235	${\tt LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpProLysMetHisThrValAsnGlyTyrValAsnG$	L
	Pmii	
793	CGCAGCCTGCCCGGCCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACCACCACCACCACCACCACCACCACCACCACC	
259	${\tt ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerValTyrTrpHisValIleGlyMetGlyThrThrough Control of the control of the$:
865	$\tt CCCGAGGTGCACAGCATCTTCCTGGAGGGCCACACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGACCACCTTCCTGGTGCGCAACCACCACCGCCAGGCCAGCCTGGACCACCACCACCACCACCACCACCACCACCACCACCAC$	3
283	${\tt ProGluValHisSerIlePheLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGluGlyHisThrPheLeuValArgAsnHisArgAsnH$	1
937	${\tt ATCAGCCCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACCCAC$	2
307	${\tt IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMetAspLeuGlyGlnPheLeuLeuPheCysHistorical} \\$	3
L009	ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCCCAGCT	3
	${\tt IleSerSerHisGlnHisAspGlyMetGluAlaTyrValLysValAspSerCysProGluGluProGlnLews} \\$	
L081	CGCATGAAGAACAACGAGGAGGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCG	C
355	${\tt ArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspLeuThrAspSerGluMetAspValValArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspLeuThrAspSerGluMetAspValValArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspLeuThrAspSerGluMetAspValValArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspAspLeuThrAspSerGluMetAspValValArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspAspLeuThrAspSerGluMetAspValValArgMetAspValArgMetAspValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValArgMetAspValValArgMetAspValValArgMetAspValValArgMetAspValValArgM$	g
	(BgIII/BamHI)	
1153	TTCGACGACAACAGCCCCAGCTTCATCCAGATCCGCAGCGTGGCCAAGAAGCACCCCAAGACCTGGGT	
	${\tt PheAspAspAspAsnSerProSerPheIleGlnIleArgSerValAlaLysLysHisProLysThrTrpValAlaBysHisProLysThrTrpValAlaBysHisProLysThrTrpValAlaBysHisProLysThrTrpValAlaBysHisProLysHisProLysThrTrpValAlaBysHisProLysThrTrpValAlaB$	
1225	CACTACATCGCCGCGAGGAGGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACCGCAGCTA	C
403	${ t His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala ProLeu Val Leu Ala ProAsp Asp Arg Ser Tyron Colon $	r
	Eagl	
1297	AAGAGCCAGTACCTGAACAACGGCCCCCAGCGCATCGGCCGCAAGTACAAGAAGGTGCGCTTCATGGCCTA	C
427	${\tt LysSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyArgLysTyrLysLysValArgPheMetAlaTy}$	r

FIG. 9A

1369 ACCGACGAGACCTTCAAGACCCGCGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGC 451 ThraspGluThrPheLysThrArgGluAlaIleGlnHisGluSerGlyIleLeuGlyProLeuLeuTyrGly

Apai

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1441 GAGGTGGGCGACACCCTGCTGATCATCTTCAAGAACCAGGCCAGCCGCCCCTACAACATCTACCCCCACGGC 475 GluValGlyAspThrLeuLeuIleIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly 1513 ATCACCGACGTGCGCCCCTGTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATC 499▶ IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle Balli 1585 CTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCCGC 523 LeuProGlyGluIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg 1657 TGCCTGACCCGCTACTACAGCAGCTTCGTGAACATGGAGCGCGACCTGGCCAGCGGCCTGATCGGCCCCCTG 547 CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu 1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCGCGAACCAGATCATGAGCGACAAGCGCAACGTGATCCTG 571 LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu 1801 TTCAGCGTGTTCGACGAGAACCGCAGCTGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGCC 595 PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla 1873 GGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTCGAC 619 GlyValGlnLeuGluAspProGluPheGlnAlaSerAsnIleMetHisSerIleAsnGlyTyrValPheAsp 1945 AGCCTGCAGCTGAGCGTGTCCCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGAC 643 SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTrpTyrIleLeuSerIleGlyAlaGlnThrAsp 2017 TTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTC 667 PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe 2089 CCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCTGGGCTGCCACAACAGC 691 propheSerGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer 2161 GACTTCCGCAACCGCGCATGACCGCCCTGCTGAAGGTGAGCAGCTGCGACAAGAACACCGGCGACTACTAC $715 \blacktriangleright \texttt{AspPheArgAsnArgGlyMetThrAlaLeuLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr}$ 2233 GAGGACAGCTACGAGGACATCAGCGCCTACCTGCTGAGCAAGAACAACGCCATCGAGCCCCCGCAGGCGCAGG 739 GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAsnAlaIleGluProArgArgArgArg 2305 CGCGAGATCACCCGCACCACCCTGCAGAGCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAG 763 ArgGluIleThrArgThrThrLeuGlnSerAspGlnGluGluIleAspTyrAspAspThrIleSerValGlu 2377 ATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCCGCAGCTTCCAGAAGAAGACC 787 MetLysLysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysLysThr 2449 CGCCACTACTTCATCGCCGCCGTGGAGCGCCTGTGGGACTACGGCATGAGCAGCAGCCCCCACGTGCTGCGC 811 ArgHisTyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerProHisValLeuArg 2521 AACCGCGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTGGTGTTCCAGGAGTTCACCGACGGCAGCTTC 835 AsnArgAlaGlnSerGlySerValProGlnPheLysLysValValPheGlnGluPheThrAspGlySerPhe Apal 2593 ACCCAGCCCTGTACCGCGGGGGGCTGAACGAGCACCTGGGCCTGCTGGGCCCCTACATCCGCGCCGAGGTG 859 ThrGlnProLeuTyrArgGlyGluLeuAsnGluHisLeuGlyLeuLeuGlyProTyrIleArgAlaGluVal 2665 GAGGACAACATCATGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGC 883 GluAspAsnIleMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSer 2737 TACGAGGAGCACCAGCGCCCAGGCCCCGCAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTAC 907 \blacktriangleright TyrGluGluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyr 2809 TTCTGGAAGGTGCAGCACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGC

931 PheTrpLvsValGlnHisHisMetAlaProThrLvsAspGluPheAspCvsLvsAlaTrpAlaTvrPheSer

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2881 GACGTGGACCTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCACCACCCTG 955 AspValAspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeu 2953 AACCCCGCCCACGGCCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAG 979 AsnProAlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLys 3025 AGCTGGTACTTCACCGAGAACATGGAGCGCAACTGCCGCGCCCCTGCAACATCCAGATGGAGGACCCCACC 1003 SerTrpTyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThr 3097 TTCAAGGAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGCCTGGTGATGGCC 1027 PheLysGluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAla Kpni 3169 CAGGACCAGCGCATCCGCTGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGC 1051 GlnAspGlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSer 3241 GGCCACGTGTTCACCGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTC 1075 GlyHisValPheThrValArgLysLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPhe 3313 GAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGTGGAGTGCCTGATCGGCGAGCACCTGCAC 1099 GluThrValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHis 3385 GCCGGCATGAGCACCCTGTTCCTGGTGTACAGCAACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGCCAC 1123 AlaGlyMetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHis Apai 3457 ATCCGCGACTTCCAGATCACCGCCAGCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCCGCCTGCACTAC 1147 IleArgAspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyr 3529 AGCGGCAGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATG 1171 SerGlySerIleAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMet 3601 ATCATCCACGGCATCAAGACCCAGGGCGCCCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATC 1195 IleIleHisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIle 3673 ATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGGCAACAGCACCGGCACCCTGATGGTGTTCTTC 1219 MetTyrSerLeuAspGlyLysLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePhe (Smal/EcoRV) 3745 GGCAACGTGGACAGCAGCGCCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCCGCTACATCCGCCTG 1243 GlyAsnValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeu 3817 CACCCCACCACTACAGCATCCGCAGCACCCTGCGCATGGAGCTGATGGGCTGCGACCTGAACAGCTGCAGC 1267 HisProThrHisTyrSerIleArgSerThrLeuArgMetGluLeuMetGlyCysAspLeuAsnSerCysSer 3889 ATGCCCCTGGGCATGGAGAGCAAGGCCATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACCAACATG 1291 MetProLeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMet 3961 TTCGCCACCTGGAGCCCCAGCAAGGCCCGCCTGCACCTGCAGGGCCGCAGCAACGCCTGGCGCCCCCAGGTG 1315 PheAlaThrTrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnVal 4033 AACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCGGCGTGACCACCCAGGGC 1339 AsnAsnProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGly 4105 GTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCCAGGACGGCCACCAGTGG 1363 ValLysSerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerSerGlnAspGlyHisGlnTrp 4177 ACCCTGTTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAAC 1387 ThrLeuPhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsn 4249 AGCCTGGACCCCCCTGCTGACCCGCTACCTGCGCATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTG 1411 SerLeuAspProProLeuLeuThrArgTyrLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeu

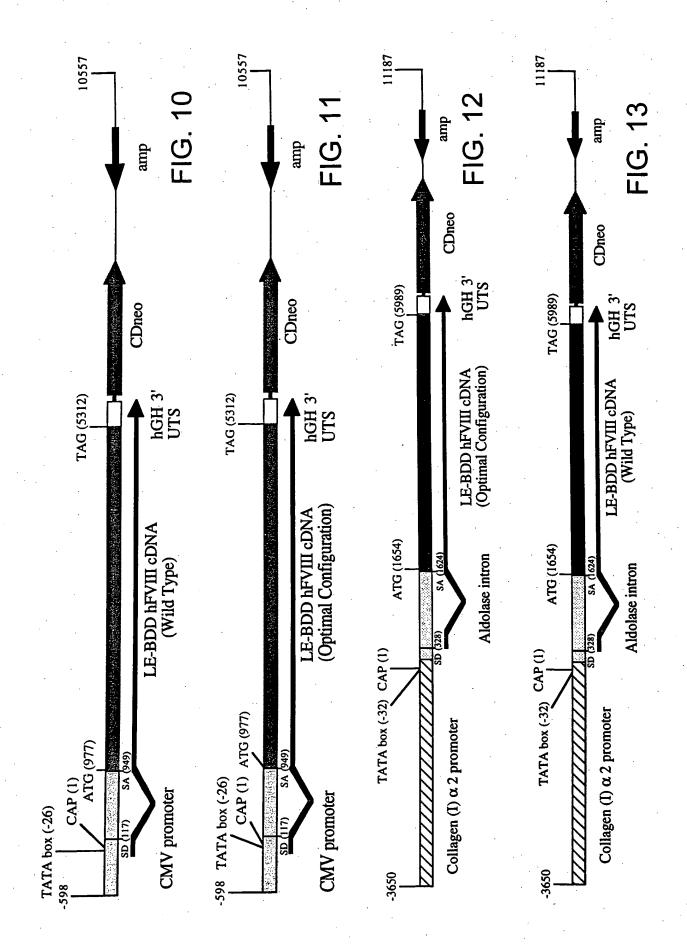
4321 CGCATGGAGGTGCTGGGGCTGCGAGGCCCAGGACCTGTACTAGCTGCCCGGGCTACAAGCTTTAC

1435 ArgMetGluValLeuGlyCysGluAlaGlnAspLeuTyr...

FIG. 9C

Hindlll

Smal



Codon Frequency in Highly Expressed Human Genes

	% occurrence			% oc	currence		% occurrence	
<u>Glu</u>			<u>Cys</u>			Gln		
GA	Α	25	TG	C	68	CA	Α	12
	G	75		T	32		G	88
								• •
Arg			<u>Ala</u>			Gly	· . :	•
CG	C	37	GC	C	53	GG	C	50
	T	7		T	17		.T	12
• • .	A	6	·	Α	13		'A	14
	G	21		G	17		G	24
AG	A	10						
	G	18						
					: *		٠.	
Leu			<u>Ser</u>			<u>Pro</u>		
CT	C	26	TC	C	28	CC	C	48
-	T	5		T	13		T	19
	Α	3		A	5		Α	16
	G	58		G	9		G	17
TT	$\mathbf{A}_{\mathbf{A}}^{\mathbf{A}}$	2	AG	Ċ	34		٠.	
	G	6		T	10			
						•		

FIG. 14A

Codon Frequency in Highly Expressed Human Genes

	% occurrence		•	% occur			-	% occurrence		
<u>Ilc</u>			<u>Thr</u>				<u>Val</u>			
AT	C	77	AC	C	57		GT	C	25	
	T	18		T	14			Ť	7	
	Α	5		Α	14			A	5	
				G	15		•	G	64	
		· .								
<u>Tyr</u>			<u>Phe</u>		•		<u>Lys</u>			
TA	C	74	TT	C.	80		AA	Α	18	
	T	26	·	T	20	·		G	82	
•		•	· · · · · ·							
<u>Asn</u>	··.		<u>His</u>				·			
AA	C	78	CA	C	79	•	٠, .			
•	T	25		T	21					
				•	•		•			

FIG. 14B

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